

# Vernakalant Hydrochloride for the Rapid Conversion of Atrial Fibrillation After Cardiac Surgery

## A Randomized, Double-Blind, Placebo-Controlled Trial

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**Background**—Postoperative atrial arrhythmias are common and are associated with considerable morbidity. This study was designed to evaluate the efficacy and safety of vernakalant for the conversion of atrial fibrillation (AF) or atrial flutter (AFL) after cardiac surgery.

**Methods and Results**—This was a prospective, randomized, double-blind, placebo-controlled trial of vernakalant for the conversion of AF or AFL after coronary artery bypass graft, valvular surgery, or both. Patients were randomly assigned 2:1 to receive a 10-minute infusion of 3 mg/kg vernakalant or placebo. If AF or AFL was present after a 15-minute observation period, then a second 10-minute infusion of 2 mg/kg vernakalant or placebo was given. The primary end point was the conversion of postcardiac surgery AF or AFL to sinus rhythm within 90 minutes of dosing. In patients with AF, 47 of 100 (47%) who received vernakalant converted to SR compared with 7 of 50 (14%) patients who received placebo ( $P<0.001$ ). The median time to conversion was 12 minutes. Vernakalant was not effective in converting postoperative AFL to sinus rhythm. Two serious adverse events occurred within 24 hours of vernakalant administration (hypotension and complete atrioventricular block). There were no cases of torsades de pointes, sustained ventricular tachycardia, or ventricular fibrillation. There were no deaths.

**Conclusions**—Vernakalant was safe and effective in the rapid conversion of AF to sinus rhythm in patients who had AF after cardiac surgery.

**Clinical Trial Registration**—clinicaltrials.gov. Identifier: NCT00125320.

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**Key Words:** atrial fibrillation ■ cardiac surgery ■ antiarrhythmic drugs

Atrial arrhythmias occur after coronary artery bypass graft (CABG) and valvular surgery in approximately 20% to 50% of patients, depending on definitions, types of surgery, and surveillance methods.<sup>1-3</sup> Atrial fibrillation (AF) is the most common atrial arrhythmia in this setting.<sup>4-6</sup> Postoperative atrial arrhythmias are associated with increased morbidity from stroke, congestive heart failure, hemodynamic compromise, and ventricular dysrhythmias and with prolonged hospitalization and increased costs and rates of rehospitalization after discharge.<sup>1,7-10</sup>

### Clinical Perspective on p 659

Current treatment strategies for post-cardiac surgery AF are similar to those for acute AF and consist of thrombolysis

prevention and various agents to control ventricular response rate and restore sinus rhythm (SR).<sup>2,11-13</sup> Currently available antiarrhythmic drugs have variable efficacy and safety profiles and may produce significant cardiac and noncardiac adverse effects. They may be contraindicated in some postoperative patients because of their negative inotropic or chronotropic effects.<sup>11,14</sup> A safe and effective agent for the rapid conversion of atrial arrhythmias to SR would benefit patients after cardiac surgery.

Vernakalant hydrochloride injection (RSD1235) is a novel, relatively atrial-selective antiarrhythmic agent for the conversion of AF to SR that acts by means of frequency-dependent blockade of Na<sup>+</sup> channels as well as blockade of early-

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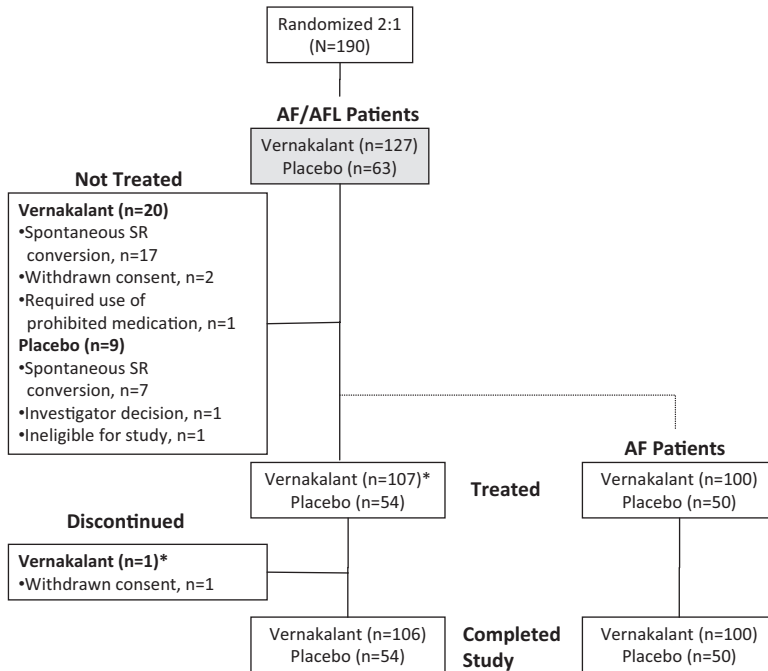
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**Figure 1.** Patient disposition. \*One patient in the vernakalant group was adjudged by the Clinical Events Committee to be in SR before and after treatment.

activating  $K^+$  channels.<sup>15</sup> In a placebo-controlled phase 2 trial ( $n=56$ ), vernakalant rapidly converted recent-onset AF (lasting 3 to 72 hours) to SR.<sup>16</sup> In addition, 2 recent placebo-controlled, phase 3 clinical studies have confirmed the efficacy and safety of vernakalant in converting recent-onset AF (lasting 3 hours to 7 days) to SR.<sup>17,18</sup> The rate of conversion of AF to atrial flutter (AFL) in these nonsurgical populations was low (5.6% and 8.6% in the phase 2 and 3 trials, respectively).<sup>16,17</sup> This study evaluated the efficacy of vernakalant in converting AF or AFL to SR in patients recovering from CABG, valvular surgery, or both.

## Methods

### Study Design

This was a phase 3, prospective, randomized, double-blind, placebo-controlled study conducted at 43 sites in Canada, the United States, Denmark, Italy, Poland, Argentina, and India. The study was approved by an institutional review board at each site, and all patients gave written informed consent.

Randomization codes were generated by an unblinded statistician who was not involved in the study operations. The unblinded pharmacist or designee at each site randomly assigned eligible patients by calling a central randomization center. All of the study staff, with the exception of the site pharmacist, were blinded to the identity of the treatment assignments. The pharmacist at each site prepared study drug or placebo as required and ensured that the volume of study treatment and the time for delivery to study personnel was equivalent, regardless of treatment assignment.

Eligible patients included men and women  $\geq 18$  years of age, with sustained AF or AFL (lasting 3 to 72 hours) occurring between 24 hours and 7 days after CABG, valvular surgery, or both. Patients were hemodynamically stable (systolic blood pressure [SBP]  $>90$  mm Hg and  $<160$  mm Hg and diastolic blood pressure  $<95$  mm Hg), weighed 45 to 136 kg (99 to 300 lb), and had documented SR before and after surgery. Women were not pregnant or nursing, and, if premenopausal, were using an effective form of birth control. Patients were excluded if they had an uncorrected QT interval  $>500$  ms; a ventricular response rate to AF  $<45$  bpm; a QRS interval  $>140$  ms without a pacemaker; second- or third-degree atrioventricular (AV) block; a history of torsades de pointes; unstable

class IV congestive heart failure; serious hepatic or renal disease; end-stage disease states; a reversible cause of AF such as hyperthyroidism or pulmonary embolism; an uncorrected electrolyte imbalance; digoxin toxicity; or had received another investigational drug or intravenous vernakalant in the 30 days before enrollment. Patients were excluded if oral amiodarone had been taken in the previous 3 months, if intravenous amiodarone had been administered in the previous 24 hours, or if class I or class III antiarrhythmic drugs had been administered after cardiac surgery. Treatment with rate control drugs, such as  $\beta$ -adrenergic-blocking agents, calcium antagonists, or digoxin, was permitted provided heart rate (HR) was  $>50$  bpm and that a loading dose or bolus supplementation of the agent was not given in the 2 hours before study drug administration.

Patients were randomly assigned 2:1 to receive either a 10-minute infusion of 3.0 mg/kg vernakalant or placebo (normal saline solution), followed by a 15-minute observation period. If the patient did not demonstrate conversion to SR, a second 10-minute infusion of 2.0 mg/kg vernakalant or placebo was administered. The infusion was discontinued if any of the following were observed: uncorrected QT interval  $\geq 550$  ms or prolongation of the uncorrected QT interval  $>25\%$ , HR  $<45$  bpm lasting  $\geq 30$  seconds with symptoms or  $<40$  bpm lasting  $\geq 30$  seconds with or without symptoms, SBP  $>190$  mm Hg or  $<85$  mm Hg or new requirement for inotropic support, new bundle-branch block or QRS interval prolongation of  $\geq 50\%$ , any polymorphic ventricular tachycardia, sinus pause of  $\geq 5$  seconds, change in cardiac rhythm or AV conduction that compromised patient safety, or any intolerable side effects. Electric cardioversion and the administration of any additional antiarrhythmic medication were withheld for at least 2 hours after dosing.

Patients were monitored at the study facility for a minimum of 24 hours after dosing. ECGs were recorded and vital signs were measured at specified intervals during the screening period, the subsequent 24 hours, on conversion to SR, at the follow-up visit scheduled at discharge (up to day 14), and at the occurrence of a serious adverse event (AE). Telemetry was performed before treatment and continuously thereafter for at least 2 hours after dosing, and Holter monitoring commenced at baseline and continued for 24 hours after dosing. AEs were recorded through the follow-up visit, and serious AEs were recorded throughout the study period, which concluded with a telephone follow-up on day 30.

### Study End Points

The prespecified primary efficacy end point was the proportion of patients with AF/AFL after CABG, valvular surgery, or both who

demonstrated conversion to SR, for a minimum duration of 1 minute, within 90 minutes of first infusion. Patients reaching this end point were categorized as responders. The secondary efficacy end points were the time to conversion of AF/AFL to SR among responders, the proportion of responders with AF and their time to conversion, and the proportion of patients with AFL who responded to treatment and their time to conversion.

Exploratory analyses included the proportion of all responders who required a single dose of study drug to demonstrate conversion, the proportion of responders who remained in SR at hour 24 and day 7, the proportion of patients with at least 1 arrhythmia symptom at each scheduled assessment and the proportion of patients who reported each symptom at each assessment, and the influence of baseline and demographic characteristics, including type of surgery, on the primary end point.

All 12-lead ECG recordings were sent to a central ECG laboratory for analysis and interpretation. All 12-lead ECGs and Holter monitor recordings were reviewed by members of a Clinical Events Committee, who were blinded to treatment, to determine the baseline arrhythmia and to assess conversion to SR. Safety was monitored by a data safety and monitoring board.

## Statistical Analysis

All statistical tests were 2-sided and conducted at the 0.05 significance level. All patients in each treatment group who received any amount of study drug were analyzed for efficacy and safety.

It was anticipated that a total of approximately 210 subjects would be randomly assigned (140 to vernakalant and 70 to placebo) in this clinical trial. Assuming a spontaneous conversion rate of 15%, this would provide 178 evaluable patients. Assuming a placebo response rate of 35%, the proposed sample size would provide 84% power to detect a minimum difference between placebo and vernakalant of 23.5% (ie, a vernakalant response rate of 58.5%). This was based on a 2-sided  $\chi^2$  test with a 5% significance level.

Demographics and baseline characteristics were compared using a 1-way ANOVA with a fixed effect for treatment for continuous variables and a Fisher exact test for categorical variables. The primary end point analysis was based on the Cochran-Mantel-Haenszel test stratified by country. Logistic regression was used to investigate the effect of various baseline and demographic characteristics on the primary end point. For the secondary end points, the Kaplan-Meier method was used to summarize the time to conversion and the log-rank test was used to compare the distributions. Comparisons of the proportion variables for the secondary end points were conducted using the same methods as used for the primary end point. The Kaplan-Meier method was used to determine the proportion of patients who remained in SR at hour 24 and day 7. A Fisher exact test was used to summarize and compare the proportion of patients reporting AF/AFL symptoms at various time points. Analysis of ECG intervals at each time point was based on an analysis of covariance with treatment as a factor and baseline as a covariate. The probability values reported are raw unadjusted probability values, which do not account for multiplicity.

## Results

### Study Population

From June 2004 to February 2007, a total of 190 patients were randomly assigned to either vernakalant or placebo (Figure 1). Twenty-nine patients did not receive study drug, including 24 patients (7 placebo and 17 vernakalant) who spontaneously converted to SR before treatment. Of the other 5 patients, 2 patients assigned to vernakalant withdrew consent and 3 patients (1 vernakalant and 2 placebo) violated inclusion or exclusion criteria. Accordingly, 161 patients (54 placebo and 107 vernakalant) received treatment and were included in the efficacy and safety analyses. Of the 161 patients treated, 150 had AF and 10 had AFL at randomiza-

**Table 1. Baseline Demographic and Clinical Characteristics**

Characteristic	Treatment Group	
	Placebo (n=54)	Vernakalant (n=107)
Men	40 (74.1)	81 (75.7)
White	50 (92.6)	101 (94.4)
Age, y	67.8±6.4	68.3±7.7
Surgery type		
CABG	37 (68.5)	71 (66.4)
Valvular	10 (18.5)	28 (26.2)
Both	7 (13.0)	8 (7.5)
Left atrial and ventricular measurements		
LVEF <50%*	12 (30.8)	31 (36.0)
Left atrial diastolic dimension	42.9±6.8	42.0±6.6
Arrhythmia		
AF	50 (92.6)	100 (93.5)†
AFL	4 (7.4)	6 (5.6)†
Hypertension‡	40 (74.1)	72 (67.3)
Ischemic heart disease‡	45 (83.3)	84 (78.5)
Heart failure‡	15 (27.8)	36 (33.6)
Concomitant therapy		
Any rate control	38 (70.4)	71 (66.4)
$\beta$ -Blockers	38 (70.4)	64 (59.8)
Calcium channel blockers	3 (5.6)	7 (6.5)
Digitalis glycosides	3 (5.6)	9 (8.4)
Any rhythm control		
Class I antiarrhythmics§	0	0
Class III antiarrhythmics	3 (5.6)	4 (3.7)

Data are presented as n (%) or mean±SD.

\*Among patients in whom LVEF was known.

†One patient given vernakalant was adjudged by the Clinical Events Committee to be in SR before and after treatment.

‡Derived from verbatim terms in medical history after study database was locked and unblinded.

§Class I antiarrhythmics included disopyramide, flecainide, procainamide, propafenone, and quinidine.

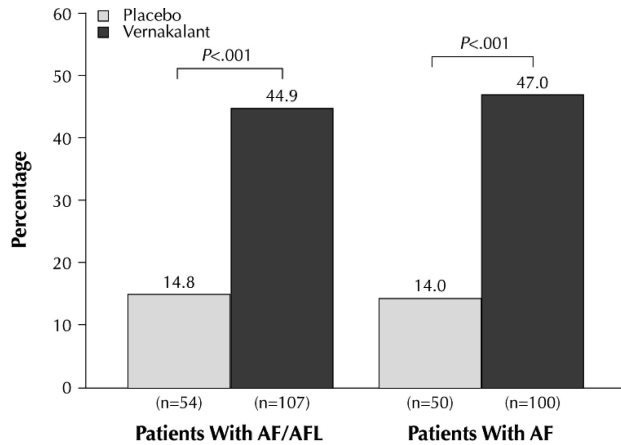
||Class III antiarrhythmics included amiodarone, dofetilide, ibutilide, and sotalol.

tion. One patient who was assigned to the vernakalant group was later adjudged by the Clinical Events Committee to be in SR before and after treatment.

The 2 treatment groups did not differ significantly in baseline demographic or clinical characteristics (Table 1). Among patients in whom left ventricular ejection fraction (LVEF) was known, the majority in both groups had a normal LVEF. Most patients had undergone CABG surgery.

### Efficacy

The primary end point, conversion of AF/AFL to SR for a minimum duration of 1 minute within 90 minutes of first infusion, was achieved in 44.9% (48 of 107) and 14.8% (8 of 54) of patients given vernakalant and placebo, respectively ( $P<0.001$ ) (Figure 2). In patients with AF at baseline, 47%



**Figure 2.** Success rates in the overall AF/AFL population and among patients with AF.

(47 of 100) of patients given vernakalant demonstrated conversion to SR, whereas only 14% (7 of 50) of patients given placebo did so ( $P<0.001$ ). Of the patients with AFL at baseline, none of the 6 given vernakalant and 1 of the 4 given placebo demonstrated conversion to SR.

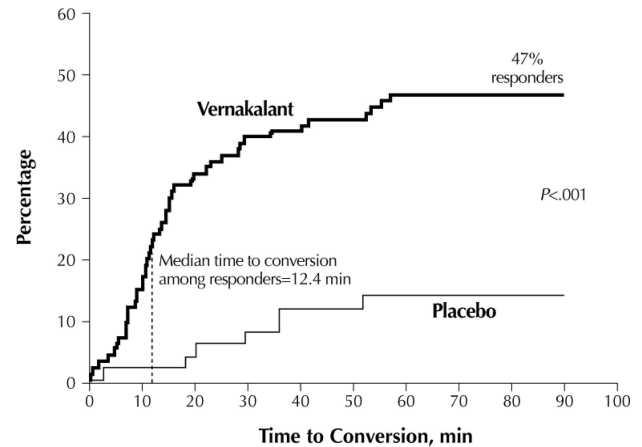
Prespecified subgroup analyses by surgery type revealed no significant differences in responder rates between patients who underwent CABG surgery and those who underwent valvular surgery (Table 2). There was a significant difference in responder rates between vernakalant and placebo in patients who underwent CABG surgery alone (34/71 [47.9%] versus 5/37 [13.5%],  $P=0.002$ ). There was no effect of age, sex, LVEF, or left atrial diastolic dimension on the probability of conversion to SR. Patients given vernakalant who received rate-control medications, however, were more likely to demonstrate conversion to SR than were patients who did not receive rate-control medications (22/41 [53.7%] versus 26/66 [39.4%],  $P=0.027$ ).

AF-to-SR conversion with vernakalant was rapid, with a 12.4-minute median time to conversion (Figure 3). Among patients with AF/AFL who responded to treatment with vernakalant, the median time to conversion was 12.3 minutes (range, 0.5 to 57.1 minute). In addition, most patients (75%) who responded to vernakalant demonstrated conversion to SR with a single dose of vernakalant. Excluding those with missing data, 60% of the 48 patients with AF/AFL who responded to vernakalant were in SR at 24 hours and 57% were in SR at day 7; only 3 responders who reverted back to AF or AFL did so within 2 hours.

**Table 2. Treatment-Associated Conversion of AF/AFL to SR by Surgery Type**

Surgery Type	Placebo, n/N (%)	Vernakalant, n/N (%)	Treatment Difference (Vernakalant/Placebo), % (95% CI)	P Value
CABG	5/37 (13.5)	34/71 (47.9)	34.4 (18.4–50.4)	0.002
Valvular	2/10 (20.0)	10/28 (35.7)	15.7 (–14.8 to 46.2)	0.562
CABG and valvular	1/7 (14.3)	4/8 (50.0)	35.7 (–7.6 to 79.0)	0.088

CI indicates confidence interval.



**Figure 3.** Cumulative responder percentage based on time after the start of treatment among patients with AF.

Regarding AF/AFL symptoms at minute 90, significantly fewer patients given vernakalant compared with placebo had rapid heartbeats (15.9% versus 46.3%, respectively,  $P<0.001$ ), palpitations (16.8% versus 44.4%,  $P<0.001$ ), and irregular pulse (22.4% versus 42.6%,  $P=0.01$ ). These results are consistent with the greater proportion of patients who received vernakalant that were in SR at minute 90.

### Safety

Serious AEs were reported for 9.3% (10 of 107) and 11.1% (6 of 54) of patients given vernakalant and placebo, respectively. Within 24 hours of dosing, 2 serious AEs occurred in patients who received vernakalant (and were considered drug related) and none occurred in patients given placebo. One patient who demonstrated conversion to SR had hypotension (arterial blood pressure of 49/39 mm Hg) 3 minutes after receiving 1 partial dose of vernakalant. This patient was treated with intravenous fluids and norepinephrine, and the event resolved 3 minutes later. Another patient had complete AV block (after conversion) during the first infusion of vernakalant. External pacing through an epicardial wire (placed at the time of surgery) was initiated, and the patient recovered 12 minutes later. There were no deaths reported in this study.

Treatment-emergent AEs occurring within 24 hours of study drug administration occurred in 38.3% (41 of 107) and 31.5% (17 of 54) of patients who received vernakalant or placebo, respectively. Of these, the most common events were AF (vernakalant, 8.4%; placebo, 9.3%) and nausea (vernakalant, 5.6%; placebo, 3.7%). Three patients in the vernakalant group (and none in the placebo group) discontinued study drug, 1 each due to hypotension (described above), complete AV block (described above), and right bundle-branch block.

It was not surprising that in this population, a small proportion of patients with AF in both groups had AFL; among patients with AF, 5 given vernakalant (5%) and 2 given placebo (4%) demonstrated conversion to AFL, all within 1 hour of infusion. Two of the patients given vernakalant and 1 given placebo later converted to SR.



**Table 3. Ventricular Arrhythmia Events, Bradycardia Events, and Hypotension Events in the First 24 Hours**

Event, n (%)	0–2 h After Dosing		2–24 h After Dosing		After Dosing	
	Placebo (n=54)	Vernakalant (n=107)	Placebo (n=54)	Vernakalant (n=107)	Placebo (n=54)	Vernakalant (n=107)
Any ventricular arrhythmia event*	2 (3.7)	5 (4.7)	7 (13.0)	16 (15.0)	9 (16.7)	19 (17.8)
Torsades de pointes	0	0	0	0	0	0
Ventricular tachycardia†	0	4 (3.7)	7 (13.0)	16 (15.0)	7 (13.0)	18 (16.8)
Ventricular fibrillation	0	0	0	0	0	0
Other rhythm‡	2 (3.7)	2 (1.9)	0	1 (0.9)	2 (3.7)	3 (2.8)
Any bradycardia event§	1 (1.9)	10 (9.3)	1 (1.9)	7 (6.5)	2 (3.7)	15 (14.0)
Any HR <40 bpm on Holter	1 (1.9)	4 (3.7)	0	0	1 (1.9)	4 (3.7)
Any hypotension event	9 (16.7)	14 (13.1)	9 (16.7)	13 (12.2)	13 (24.1)	23 (21.5)
SBP <90 mm Hg	0	6 (5.6)	0	3 (2.8)	0	8 (7.5)

\*Derived from AEs, Holter monitoring, and 12-lead ECGs. Patients may have had >1 event.

†Wide-complex beats ( $\geq 3$  beats) with an HR  $\geq 100$  bpm.

‡Other rhythm includes aberrant pair, ventricular pair, and ventricular bigeminy.

§Incidence based on combined analysis of AEs, 12-lead ECGs, including sinus bradycardia (HR <60 bpm) and Holter monitoring.

||Incidence based on combined analysis of AEs and vital signs assessments (SBP <90 mm Hg, SBP decrease from baseline  $\geq 30$  mm Hg, diastolic blood pressure decrease  $\geq 15$  mm Hg).

In the first 2 hours and 24 hours after the start of dosing, the incidence of all ventricular arrhythmia events was similar in both treatment groups (Table 3), including 4 patients given vernakalant who developed nonsustained ventricular tachycardia in the first 2 hours, lasting 3 to 12 beats. The nonsustained polymorphic ventricular tachycardias did not resemble torsades de pointes morphologically. In addition, there were no marked increases in QT interval or typical variations in R-R interval (pause-dependent sequences) during the arrhythmia initiation to suggest torsades de pointes. These arrhythmias were identified by Holter monitoring and 12-lead ECG data, and none were reported as AEs. Over the same observation periods, bradycardia events occurred more often in the vernakalant group (Table 3). Few patients had an HR <40 bpm, and the incidence of an HR <40 bpm was similar among the vernakalant and placebo groups. Although the incidence of hypotension events was similar among treatment groups, more patients given vernakalant had a SBP <90 mm Hg. There were no cases of torsades de pointes, sustained ventricular tachycardia, or ventricular fibrillation in either treatment group.

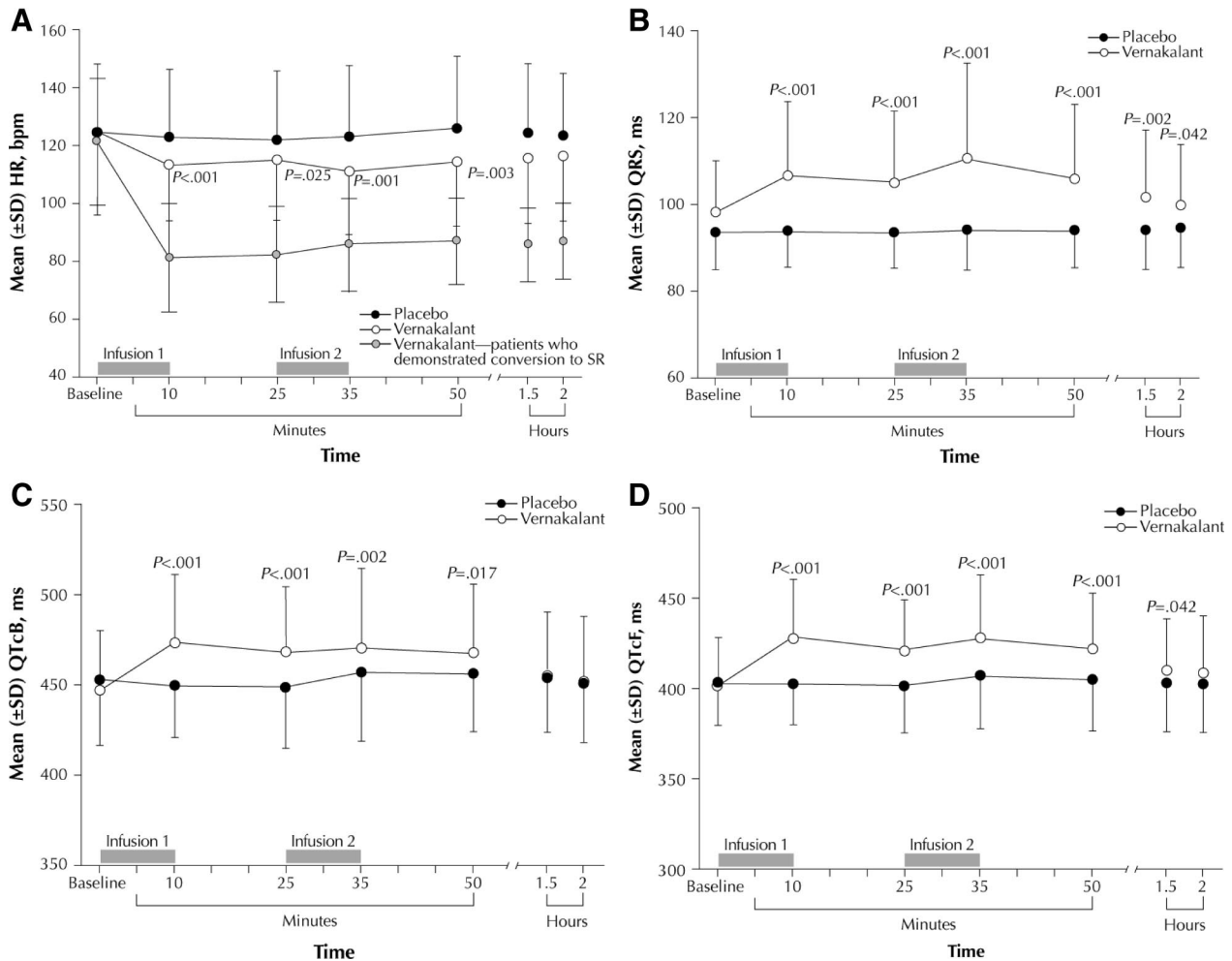
### Vernakalant and ECG Parameters

The mean  $\pm$  SD HR among all patients given vernakalant fell from  $122 \pm 26$  bpm at baseline to  $105 \pm 23$  bpm 10 minutes after initiation of treatment. This was largely accounted for by the reduction in HR among patients who demonstrated conversion to SR (Figure 4A). Among those given vernakalant who remained in AF or AFL, the decrease in HR, although significantly different from placebo through minute 50 and remaining essentially the same through hour 2, was smaller (Figure 4A). In patients who demonstrated conversion to SR with vernakalant, from baseline to the end of the first infusion, the mean QRS interval increased from

$101.0 \pm 14.9$  to  $106.6 \pm 16.1$ , and the mean Fridericia-corrected QT interval (QTcF) increased from  $407.3 \pm 25.1$  to  $426.0 \pm 30.4$  ms. The mean Bazett-corrected QT interval (QTcB) decreased from  $454.6 \pm 27.3$  ms to  $445.6 \pm 34.8$  ms.

To avoid the potential confounding effects on QRS and QT intervals caused by reductions in HR after conversion to SR, the effects of vernakalant on ECG parameters were also compared with placebo in patients who remained in AF or AFL. Among nonresponders, vernakalant prolonged QRS intervals from a baseline value of  $99.7 \pm 12.2$  ms to a peak of  $110.0 \pm 22.2$  ms at the end of second infusion. Increases from baseline in QRS intervals were significantly greater with vernakalant than with placebo at all times from 10 minutes to 2 hours (Figure 4B). Maximum increases from baseline in mean QTcB and QTcF with vernakalant in patients who remained in AF/AFL occurred at the end of first infusion, and these increases were significantly greater with vernakalant than with placebo from minutes 10 to 50 (Figure 4C and D). The minute-90 QTcF difference from baseline was also significant.

Among the 93 patients given vernakalant and 44 given placebo, with QT measurements taken at baseline and at 10 minutes, 28% and 7%, respectively, had a QTcB >500 ms at the end of first infusion. If patients with baseline QTcB >500 ms are excluded, these percentages fall to 24% with vernakalant and 2% with placebo. Within 90 minutes, the percentage of patients with a QTcB >500 ms in the 2 treatment groups was similar (7% vernakalant versus 10% placebo for all patients; 4% and 8%, respectively, for patients with baseline QTcB  $\leq 500$  ms). For QTcF, 3% of patients given vernakalant and none of the patients given placebo had values >500 ms at the end of first infusion, all of whom had baseline values  $\leq 500$  ms. Within 90 minutes, none of the patients in either treatment group had QTcF >500 ms.



**Figure 4.** Time course of changes from baseline in HR and QRS, QTcB, and QTcF for patients with AF/AFL given vernakalant compared with patients given placebo. Data (mean±SD) are shown for patients who remained in AF or AFL, except in A, which includes vernakalant-treated patients who demonstrated conversion to SR (wide error bars).

## Discussion

After cardiac surgery, postoperative AF is still common despite use of  $\beta$ -blockers and other measures of prophylaxis, and it often develops in patients with comorbidities predisposing to prolonged hospitalization.<sup>7</sup> The incidence of postoperative AF is also rising, possibly due to the increasing age of cardiac surgical patients.<sup>2</sup> According to recent guidelines for AF management, it is reasonable to restore SR in patients who have AF after cardiac surgery (level of evidence: B) with pharmacological treatments, which are more commonly used than electric cardioversion.<sup>2,7,19</sup> Moreover, several studies have demonstrated an increased risk of stroke in patients after CABG.<sup>20,21</sup> Therefore, anticoagulation is appropriate when AF persists 48 hours or longer.<sup>2</sup> Anticoagulation after cardiac surgery can also be hazardous, making prompt restoration of SR all the more reasonable.

Despite the prevalence and importance of AF secondary to cardiac surgery, few randomized, placebo-controlled studies have evaluated the efficacy of antiarrhythmic agents for restoring SR in patients after cardiac surgery.<sup>13,14</sup> Ibutilide was shown to be more effective than placebo in converting post-cardiac surgery AF or AFL to SR; in that study,

however, polymorphic ventricular tachycardia, both sustained and nonsustained, was reported in approximately 2% of patients, which has limited its usefulness.<sup>14</sup> Amiodarone is frequently used intravenously, but evidence to support its efficacy for this indication is scarce. Furthermore, clinicians may be reluctant to use electric cardioversion because of the mandate for anesthesia.

Nevertheless, it is deemed advisable by guidelines to restore SR in patients with postoperative AF that is complicated by significant symptoms, hemodynamic instability, or a contraindication to anticoagulant therapy.<sup>13</sup> In all cases, the choice of drug should be based on individual patient characteristics.<sup>13</sup>

In the present study, vernakalant was significantly more effective in rapidly converting AF to SR in patients with sustained AF that began 24 hours to 7 days after CABG, valvular surgery, or both. Treatment-associated conversion was demonstrated in 47% of vernakalant and 14% of placebo patients. AF to SR conversion with vernakalant was rapid, with a median time to conversion of 12 minutes, and 75% of responders required only 1 dose of vernakalant. Significantly fewer patients given vernakalant had rapid heartbeats, palpitations, and irregular pulse rates compared with those given placebo. In 6 patients with AFL at baseline, vernakalant did

not convert the arrhythmia to SR. Although there were too few patients with AFL to draw any firm conclusions in the postoperative population, vernakalant has not proven effective in converting AFL to SR in any study to date.<sup>18</sup> Effectiveness for AFL conversion may require more potent  $I_{Kr}$  block, as with ibutilide.<sup>14</sup> There were no significant differences in treatment-associated conversion rates among those who underwent CABG or valvular surgery alone, although the number of patients with valvular surgery was small.

Patients given vernakalant who remained in AF or AFL had significant increases in QRS, QTcB, and QTcF intervals, with the latter 2 returning to placebo levels within 2 hours. In those who remained in AF or AFL, vernakalant also had a small but significant HR-lowering effect, which dissipated within 90 minutes. These observations probably are caused by  $K^+$  channel blockade (which occurs predominantly in the atria but also affects the ventricles),  $Na^+$  channel blockade, and modest AV-nodal-blocking effects of vernakalant.<sup>22</sup> Patients given vernakalant did have a higher incidence of bradycardia events, but this probably is related to the high rate of SR conversion with vernakalant and the subsequent large drop in HR.

Vernakalant was well tolerated. Only 2 patients in the vernakalant group discontinued because of serious AEs within 24 hours of treatment; each patient recovered without sequelae. One of these patients had hypotension during the initial vernakalant infusion. The infusion was discontinued; saline and norepinephrine were given and the event resolved 3 minutes after onset. Hypotension with vernakalant infusion typically occurs during or immediately after the infusion, is generally transient, and responds to saline.<sup>17</sup> A similar incidence of ventricular arrhythmia events was reported in the placebo and vernakalant groups in the 24 hours after dosing, and there were no cases of sustained ventricular tachycardia, torsades de pointes, or ventricular fibrillation in either group.

The primary limitation of this study is the population sizes. The total population and the CABG surgery population (67% of the total) were sufficient for the overall analysis and the CABG subgroup analysis. However, too few patients had valvular surgery or both CABG and valvular surgery, so the effect of vernakalant in those subgroups is not entirely clear. Further study of vernakalant in these situations is warranted. In conclusion, similar to findings from earlier phase 3 trials in patients with AF in other settings,<sup>17,18</sup> this study demonstrated that vernakalant was safe and effective for AF-to-SR conversion in patients after cardiac surgery.

## Appendix

List of Committees, Centers, and Investigators.

Steering Committee: P. Dorian, P. Kowey, L.B. Mitchell, C. Pratt, D. Roy, P. Schwartz, E. Toft; Data Safety Monitoring Board: J. Camm, D. DeMets, L. Køber, J.Y. Le Heuzey, A. Waldo; Clinical Events Committee: K. Egstrup, L. Erhardt, M. Hamer, E. Pritchett; Center, City, Investigator: Argentina: Sanatorio Mitre, Buenos Aires, Blumberg; Fundacion Favaloro, Buenos Aires, Figal; Instituto Cardiovascular de Buenos Aires, Buenos Aires, Giniger; Hospital San Juan de Dios, La Plata, Lolo; Instituto Cardiovascular Integral Denton Cooley, Buenos Aires, Rabinovich; Canada: Queen Elizabeth II Health Sciences Center, Halifax, Basta; Hamilton Health Sciences General Site, Hamilton, Connolly; Hopital Notre-Dame du

CHUM, Montreal, Coutu; St Michael's Hospital Department of Cardiology, Toronto, Dorian; University of Ottawa Heart Institute, Ottawa, Green; Libin Cardiovascular Institute of Alberta, Calgary, Mitchell; Hotel Dieu, Montreal, Phaneuf; Montreal Heart Institute, Montreal, Talajic; Denmark: Gentofte Amtssygehus, Hellerup, Aggestrup; Odense Universitetshospital Thoraxkirurgisk Afdeling T, Odense C, Andersen; Aalborg Sygehus Thoraxkirurgisk Afdeling, Aalborg, Jorgensen; Rigshospitalet Thoraxkirurgisk Klinik RT, København Ø, Olsen; India: Escorts Heart Institute and Research Center, New Delhi, Kler; Narayana Hrudalaya Department of Cardiothoracic Surgery, Bangalore, Kumar; Fortis Heart and Multispecialty Hospital, Mohali, Mahant; Amrita Institute for Medical Sciences, Kerala, Nair; Madras Mission Hospital Department of Cardiothoracic Surgery, Chennai, Rajan; Asian Heart Institute, Mumbai, Rane; CARE Hospital Department of Cardiothoracic Surgery, Hyderabad, Rani; Italy: Divisione Di Cardiocirurgia Clinica Gavazzeni-Humanitas, Bergamo, Gerometta; Divisione di Cardiologia, Padova, Ilceto; Unità Operativa di Cardiocirurgia Dipartimento Cardio Toracico, Pisa, Minzioni; Dipartimento Di Cardiologia Policlinico San Matteo, Pavia, Schwartz; Poland: Department of Cardiac Surgery, 1st Chair of Cardiology and Cardiac Surgery, Medical University of Lodz, Banach; I Klinika Kardiocirurgii Gornoslaskie Centrum Medyczne; Slaskiej, Katowice, Bochenek; Klinika Chirurgii Serca, Naczyn i Transplantologii, Krakow, Sadowski; Instytut Kardiologii, Warsaw, Stepinska; Katedra i Oddzial Kardiologii I, Zabrze, Zembala; United States of America: St Lukes Hospital, Duluth, Boylan; Main Line Health Center, Wynnewood, Ferdinand; The Greater Ft Lauderdale Heart Group, Ft Lauderdale, Gellman; Thoracic and Cardiovascular Healthcare Foundation, Lansing, Ip; Emory University Hospital Department of Anesthesiology, Atlanta, Levy; Duke University Medical Center, Durham, Lowe; Wisconsin Center for Clinical Research (WCCR), Milwaukee, Niazi; Florida Heart Institute, Orlando, Pollak; Sterling Research Group Ltd, Cincinnati, Roth; Marshfield Clinic, Marshfield, Vidaillet.

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Dr Kowey received consultant fees from Cardiome Pharma Corp and Astellas Pharma US, Inc. Drs Dorian and Mitchell received consultant fees from Cardiome Pharma Corp. Dr Pratt received consultant fees from Cardiome Pharma Corp and Astellas Pharma US, Inc. Dr Roy received consultant fees from Cardiome Pharma Corp and Astellas Pharma US, Inc, and is a member of the scientific advisory board for Cardiome Pharma Corp. Drs Schwartz and Toft received consultant fees from Cardiome Pharma Corp.

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- lines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–e354.
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### CLINICAL PERSPECTIVE

Atrial fibrillation (AF) occurring after cardiac surgery is common and is associated with considerable morbidity. Early restoration of sinus rhythm is usually desirable, and pharmacological conversion is generally preferable to electrical cardioversion in these early postoperative patients. Intravenous vernakalant, a new antiarrhythmic agent with atrial selective properties, has been shown to be effective in rapidly and safely converting approximately 50% of patients with new-onset AF. In this study, vernakalant demonstrated successful conversion of AF to sinus rhythm in 47% of patients with new-onset AF after cardiac surgery. Responders converted rapidly (median time, 12 minutes). Vernakalant was ineffective at converting a small number of patients (n=6) with new-onset atrial flutter. Two serious adverse events occurred during the initial 10-minute vernakalant infusion. One event of hypotension responded to discontinuation of the infusion, intravenous fluids and norepinephrine, resolving in 3 minutes. The other event was complete heart block that responded to discontinuation of the infusion and pacing through an epicardial wire (placed at the time of surgery), resolving in 12 minutes. Vernakalant does not appear to promote ventricular arrhythmia. Episodes of asymptomatic, nonsustained ventricular runs were captured on Holter monitoring in all patients given vernakalant or placebo. There were no episodes of torsades de pointes, ventricular fibrillation, or death. Vernakalant is potentially a safe and effective pharmacological alternative for the conversion of AF to sinus rhythm in patients after cardiac surgery.



## Vernakalant Hydrochloride for the Rapid Conversion of Atrial Fibrillation After Cardiac Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial

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